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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,302	09/15/2005	Michael Hagen	AM100485	5958

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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,302	HAGEN, MICHAEL	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-101* is/are pending in the application.

4a) Of the above claim(s) *12-51 and 63-101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 52-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. The amendment filed December 9, 2008 has been entered. Claims 10 and 61 have been amended. Claims 12-51 and 63-101 are withdrawn. Claims 1-11 and 52-62 are under consideration in this office action.

Specification

2. The use of the trademarks STIMULON™, QS-21™, and MPL™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Withdrawal of Rejections

3. The rejection of claims 10 and 61 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicants' amendments and arguments.

Response to Arguments

4. Applicant's arguments filed December 9, 2008 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. The rejection of claims 52-62 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

The preamble of the claims is drawn to a method of immunizing a mammalian host; however the recited steps within the method do not state what the host is immunized from. Applicants argue that there is no limitation on what the host is immunized against. However, this argument is not persuasive. The issue is that the metes and bounds of the claims are indefinite and applicants assert that there is no limitation; therefore the rejection is maintained. There is no correlation step which correlates the cholera holotoxin and the covalently associated antigen to immunizing the host against a particular antigen. Applicants' arguments are not found persuasive and the rejection is maintained.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29

USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. The double patenting rejection of claims 1, 8, 9, 52, 56, 59, 60 and 62 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 10, 13, 14,15, 24 and 25 of U.S. Patent No. 7,384,640 in view of Agren et al., (J. of Immunol. 1999. 162(2): 2432-2440) is maintained for reasons already of record.

The rejection was on the grounds that it would have been prima facie obvious at the time of applicants' invention to apply Agren et al's covalently associated cholera holotoxin to US Patent 7,384,640's composition comprising a cholera holotoxin (CT) and an antigen, wherein the CT comprises an A subunit (CT-A) having a mutation of at least amino acid 29, wherein the mutation is not an aspartic acid, wherein the CT increases immunogenicity of the antigen, and method of immunization in order to provide novel immunomodulators constructed as covalently associated holotoxin and antigens which target powerful bacterial enzymes.

The examiner acknowledges applicants request that the rejection be held in abeyance until patentable subject matter is determined. However the rejection will be maintained until the double patenting issue is resolved.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The rejection of claims 1-11 and 52-62 under 35 U.S.C. 103(a) as being unpatentable over Holmes and Jobling et al., (WO 00/18434) in view of Agren et al., (J. of Immunol. 1999. 162(2): 2432-2440) is maintained for reasons of record.

The claims are drawn to an immunogenic composition comprising a cholera holotoxin (CT) and an antigen covalently associated with the CT, wherein the CT comprises an A subunit (CT-A) having a mutation of at least amino acid residue 29 of SEQ ID NO:2, wherein the mutation is not an aspartic acid, wherein the CT increases immunogenicity of the antigen and to a method of immunizing a mammalian host comprising administering to the host an immunogenic amount of a composition comprising a cholera holotoxin (CT) and an antigen covalently associated with the CT, wherein the CT comprises an A subunit (CT-A) having a mutation of at least amino acid

residue 29 of SEQ ID NO:2, wherein the mutation is not an aspartic acid, wherein the CT increases immunogenicity of the antigen.

The rejection was on the grounds that it would have been prima facie obvious at the time of applicants' invention to apply Agren et al's covalently associated mutant cholera holotoxin and antigen to Holmes and Jobling et al., immunogenic composition comprising a cholera holotoxin (CT) and an antigen, wherein the CT comprises an A subunit (CT-A) having a mutation of at least amino acid 29 of SEQ ID NO:2, wherein the mutation is not an aspartic acid, wherein the CT increases immunogenicity of the antigen, and method of immunization in order to provide novel immunomodulators constructed as gene fusion proteins that target powerful bacterial enzymes.

Response to Arguments

9. Applicant's arguments have been fully considered but they are not persuasive.

Applicants' argue that Agren et al., teach an enhanced immune response to the conjugated adjuvants when co-administered with different antigens, the combination of two adjuvants and the combination's enhanced ability to immunomodulate, while Applicant's claimed invention is a mutated CT covalently associated with a number of different, separate antigens, not another adjuvant. In response to applicant's arguments against the Agren reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

It is noted that applicants argue that Holmes and Jobling et al., in view of Agren et al., do not teach a cholera toxin (CT) and an antigen covalently associated with the CT, however page 20, lines 1-3 of the instant specification state that where one or more antigens are conjugated (i.e., covalently associated), conjugation may be any chemical method, process or genetic technique commonly used in the art. The instant specification discloses that conjugation techniques are well known in the art (page 20, lines 24-25).

Holmes and Jobling et al., teach a composition comprising a mutant form of the Cholera toxin (CT) holotoxin that has reduced toxicity, a point mutation an amino acid 29 of the A subunit and enhancement in a host to the selected antigen. Holmes and Jobling et al., teach compositions further comprising diluent or carriers along with co-administered vaccine antigens are from a wide variety of pathogenic microorganisms. Agren et al., teach the adjuvanticity of the Cholera Toxin A1-based gene fusion protein; wherein the cholera and the antigen are covalently associated. Agren et al., teach a major breakthrough in immunomodulation and vaccine adjuvant design where they constructed a gene fusion that combined the enzymatic activity with cell targeting. Therefore contrary to applicants assertions, one of ordinary skill in the art would have a reasonable expectation of success by incorporating covalently associated mutated CT and an antigen, because no more than routine skill would have been required to covalently associated the CT and the antigen when the art already teaches co-

administration; the avoidance of harmful side effects; and the diverse application for vaccine development to advantageously achieve increased immunogenicity while maintaining reduced toxicity.

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by well known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Therefore applicants' arguments are not found persuasive and the rejection is maintained.

Conclusion

10. No claims allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645